

# Renoprotective effects of 3 HMG reductase blockers in elderly patients with acute coronary syndrome undergoing revascularization through percutaneous coronary intervention

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*Efectos renoprotectores de 3 bloqueadores de reductas de HMG en pacientes mayores con síndrome coronario agudo en revascularización mediante intervención coronaria percutánea*

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## Abstract

**T**his literature review presents current data on statins as anti-inflammatory agents in atherogenesis. Molecular mechanisms responsible for the anti-inflammatory effects of statins and clinical data on the non-lipid-lowering, anti-inflammatory effect of statins on cardiovascular outcomes are described. Analyzed the results of several randomized clinical trials, including GREACE, ALLIANCE, TNT, PLANET I, PLANET II, as well as other studies and meta-analyses. Since, cardiovascular events and renal dysfunction are associated with increased morbidity, lower quality of life and higher mortality rates. The results of statin therapy in recent large randomized clinical trials are also discussed. Prospects for further studies to compare the clinical efficacy of statins in situations where there is a risk of kidney damage are discussed. The question of preliminary (load) administration of statins in patients with the acute coronary syndrome with ST-elevation remains relevant (STEMI).

**Keywords:** acute coronary syndrome, statins, chronic kidney disease.

## Resumen

**E**sta revisión de la literatura presenta datos actuales sobre las estatinas como agentes anti-inflamatorios en la aterogénesis. Se describen los mecanismos moleculares responsables de los efectos antiinflamatorios de las estatinas y los datos clínicos sobre el efecto antiinflamatorio no reductor de lípidos de las estatinas en los resultados cardiovasculares. Se analizaron los resultados de varios ensayos clínicos aleatorios, incluidos GREACE, ALLIANCE, TNT, PLANET I, PLANET II, así como otros estudios y metanálisis. Desde entonces, los eventos cardiovasculares y la disfunción renal se asocian con una mayor morbilidad, menor calidad de vida y mayores tasas de mortalidad. También se discuten los resultados del tratamiento con estatinas en los grandes ensayos clínicos aleatorizados recientes. Se discuten las perspectivas de estudios adicionales para comparar la eficacia clínica de las estatinas en situaciones donde existe un riesgo de daño renal. La cuestión de la administración preliminar (de carga) de estatinas en pacientes con síndrome coronario agudo con elevación del ST sigue siendo relevante (STEMI).

**Palabras clave:** síndrome coronario agudo, estatinas, enfermedad renal crónica.

**C**urrently, cardiovascular diseases (CVDs) are the first cause of death in the Russian Federation and account for 56.8% of all deaths. The problem of adequate medical management of older patients is of great importance<sup>1</sup>. This is due to the existing objective patterns of pharmacodynamics and pharmacokinetics of drugs in the elderly and senile patients, the need to use special drug forms, making them more accessible to elderly patients, who suffer, as a rule, from pathology of the organ of vision, small joints of the hand with a decrease in its function, and cognitive disorders<sup>2</sup>. An important aspect of the use of drugs in geriatrics is often a low level of patient adherence thereto, a low level of awareness of the specifics of geriatric therapy among doctors of the primary medical network<sup>3</sup>. All of the above can be fully attributed to such an important group of drugs like statins.

**Main Part:** There is an opinion that using statins for primary prevention is recommended for people at risk of CVDs due to atherosclerosis, when it is 7.5% or more. This means that most men over 60 and women over 70 may have indications for taking statins. Moreover, the results of a recently published analysis indicate that only 23.6% of adults, whose average age is  $61.1 \pm 6.9$  years, did not have formal indications for taking statins, which would be based on modern clinical guidelines or results of randomized clinical trials (RCT). Concerning the expansion of indications for the use of statins, both more intensive and less intensive statin regimens have come to the attention of doctors and researchers again. The HOPE-3 study (Heart Outcomes Prevention Evaluation 3)<sup>4</sup>, which included patients without CVDs, who had an average risk of developing CVD complications, as well as the moderate level of blood lipids and blood pressure, indicated that taking rosuvastatin 10 mg/day compared with placebo for an average of 5.6 years resulted in a decrease in concentration of cholesterol (CH) of low-density lipoprotein (LDL) by 26.5% and in a statistically significant decrease in the first main composite mortality from CVD complications (CVDs), the rate of development of non-lethal myocardial infarction or non-fatal stroke by 24% (risk ratio 0.76 with a 95% confidence interval from 0.64 to 0.91;  $p = 0.002$ ).

Acute coronary syndrome (ACS) is one of the main causes of mortality due to cardiovascular disease. It should be noted that cardiovascular events and renal dysfunction are associated with increased morbidity, reduced quality of life and higher mortality rates<sup>5,6</sup>. Several risk factors have been identified in renal failure against a background of cardiovascular events: dyslipidemia, hypertension, and diabetes<sup>7</sup>.

Along with the lipid-lowering action, numerous pleiotropic (non-lipid) effects of statins have been established, including: the effect on oxidized lipoproteins; improved

endothelial function; reduced cell adhesion; anti-inflammatory effect; inhibition of proliferation and migration of smooth muscle cells; stabilization of atherosclerotic plaque; decreased platelet aggregation; improvement of the fibrinolytic system; impact on other organs and systems (prevention of osteoporosis, bone fractures; reduction of cholesterol bile saturation, dissolution of cholesterol stones, a tendency to decrease in carcinogenicity, prevention of Alzheimer's disease and vascular dementia)<sup>8,9</sup>. Statins can have an anti-atherosclerotic effect regardless of their lipid-lowering action. Since metabolism of mevalonate creates a series of isoprenoids, vital for various cellular functions - from the synthesis of cholesterol (CH) to controlling cell growth and differentiation, inhibition of HMG-CoA reductase has favorable pleiotropic effects. Therefore, statins significantly reduce the incidence of diseases of coronary arteries, play a role in both primary and secondary prevention, being the most effective lipid-lowering compounds that reduce mortality in patients with coronary disease. The analysis of direct clinical factors affecting the incidence of renal diseases showed that plasma lipid concentration is not of key importance. Statins have pleiotropic effects, and some of their actions may be mediated in other ways.

In recent years, synthetic statins (atorvastatin, rosuvastatin) have attracted the attention of researchers. Based on the structure and origin of the two drugs, it seems impossible today to identify the most effective of them. In this regard, it is necessary to focus on how they differ from each other in their absorption and distribution in the body, as well as the effectiveness of their impact on the level of cholesterol (CH) and lipoproteins of various densities with a personalized approach in certain categories of patients. At the same time, statins, through a variety of mechanisms, can have a significant protective effect on the functional abilities of the kidneys<sup>10</sup>. We should note that synthetic statins differently affect renal function, as evidenced by the results of direct and indirect comparisons of atorvastatin and rosuvastatin. Significant renal protection property of atorvastatin is confirmed by the results of several RCTs, including GREACE, ALLIANCE, TNT, PLANET I, PLANET II, as well as other research and meta-analyses. GREACE (GREEK Atorvastatin and Coronary heart disease Evaluation)<sup>11</sup> showed that atorvastatin significantly increased the creatinine clearance (CC) by 12% of baseline in patients with dyslipidemia with coronary artery disease (CAD) and initially normal kidney function, and reduced CC by 5.2% in patients not treated with statins. Thus, GREACE proved that atorvastatin has renal protective effects in patients with stable coronary artery disease (CAD) and showed that these effects are more pronounced in patients with initially reduced renal function, that they depend on the dose of the drug, and that atorvastatin increases CC more than other statins (simvastatin, pravastatin, fluvastatin)<sup>12</sup>. The ALLIANCE study (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events) involved an assessment of the change in the level of the estimated glomerular filtration rate in patients receiving atorvastatin

during 4 years of follow-up compared with standard treatment. Atorvastatin has been found to protect renal function and slow the progression of chronic kidney disease (CKD) and significantly delayed the development of the first cardiovascular complication compared with standard therapy<sup>12,13</sup>. A large-scale meta-analysis of 27 studies that included data on 39,704 patients found that statin therapy causes a statistically significant slowdown in the rate of decrease in the estimated glomerular filtration rate. At the same time, the analysis by subgroups showed that the use of atorvastatin is associated with a significantly more pronounced positive effect on the renal function compared to other statins. A large double-blind RCT - TNT that included 10,001 patients with CAD and LDL CH <130 mg/dl<sup>14</sup> compared the effects of low (10 mg/day) and high (80 mg/day) doses of atorvastatin on the change in the level of the estimated glomerular filtration rate. Thus, the TNT study showed that atorvastatin 80 mg/day has a significantly more pronounced renal protective and cardioprotective effects compared with atorvastatin 10 mg/day, especially in patients with advanced CKD<sup>15</sup>. The idea of positive renal effects of atorvastatin was confirmed in studies assessing the effects on proteinuria. For example, the works by Bianchi S. et al. showed that patients with CKD, proteinuria, and hypercholesterolemia who received an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for a year have a decrease in their level of proteinuria after a year in the atorvastatin group from 2.2 to 1.2 g/day, and from 2.0 to 1.8 g/day in the control group that did not receive atorvastatin. During the same time, there was a slight change in CC (from 51.0 to 49.8 ml/min) in the atorvastatin group and a significant decrease (from 50.0 to 44.2 ml/min) in the control group<sup>16</sup>.

The renal protective effects of atorvastatin and rosuvastatin were compared in two RCTs - PLANET I and PLANET II<sup>17</sup>, which included patients with initial moderate proteinuria and hypercholesterolemia with diabetes mellitus. The drugs were compared in high dosages, so the target dose of atorvastatin was 80 mg/day and rosuvastatin 40 mg/day; the observation period was 52 weeks. The results of the study showed that the studied drugs had a different effect on kidney function: atorvastatin in both studies significantly reduced the severity of proteinuria (on average by 15% in PLANET I and more than 20% in PLANET II), while rosuvastatin did not affect it in PLANET I or its effect was not statistically significant in the PLANET II study. The effect of statins on the glomerular filtration rate (GFR) was also different: in the atorvastatin groups, the change was statistically insignificant, whereas rosuvastatin 40 mg/day reduced GFR (statistically significant decrease in GFR in PLANET II among patients without diabetes mellitus). In addition to these effects, in PLANET I with the use of rosuvastatin, an increase in the frequency of kidney complications was noted against the background of good general tolerability of therapy (a 4-fold increase in the risk of developing acute renal failure and a 5-fold increase in the risk of doubling serum creatinine levels compared to 80 mg/day atorvastatin therapy. Thus, the PLANET I and

PLANET II RCTs showed that high doses of atorvastatin significantly reduce the severity of proteinuria (decrease by 20%) without adverse effects on the renal function, while rosuvastatin therapy leads to a significant reduction in renal function without reducing the severity of proteinuria<sup>17</sup>.

Assessment of the effect of rosuvastatin on renal function in other studies showed results that are largely comparable with data from the PLANET I and II RCTs. Two studies - POLARIS and SOLAR, which compared atorvastatin and rosuvastatin in patients with hypercholesterolemia, showed that rosuvastatin increased the severity of proteinuria to a greater extent than atorvastatin<sup>18,19</sup>. Also, in two placebo-controlled studies involving patients with chronic heart failure - GISSI-HF and CORONA, rosuvastatin therapy caused a 5-fold increase in the incidence of renal failure in the CORONA study<sup>20</sup> and a numerically higher incidence of renal dysfunction, acute renal failure, and a 2-fold increase in serum creatinine in GISSI-HF<sup>21</sup>. Finally, a post-registration analysis of the effects of rosuvastatin revealed a higher risk of developing proteinuria, nephropathy, renal failure, toxic liver damage, muscle toxicity, and rhabdomyolysis during treatment with rosuvastatin compared to other statin drugs<sup>22</sup>.

Previously, clinical practice guidelines suggested using target values for LDL cholesterol, which require repeated measurements. An escalation of treatment with higher statin doses could be a result of unmet targets of LDL cholesterol. The KDIGO (Kidney Disease: Improving Global Outcomes) research group did not recommend this strategy, as higher doses of statins have not been proven in terms of GFR safety. Since LDL levels do not necessarily indicate the need to increase statin doses, subsequent measurement of lipid levels is not recommended.

Patients with ST-segment elevation myocardial infarction (STEMI) showed that a preliminary (loading) high dose of atorvastatin prevented contrast-induced nephropathy (CIN) and protect kidney function after emergency PCI<sup>20</sup>.

To compare statins, a post-hoc analysis combined data from PLANET I with data from PLANET II. Although rosuvastatin in a high dose reduces plasma lipid concentrations to a greater extent than a high dose of atorvastatin, atorvastatin appears to have a higher renal protective effect for the studied CKD population<sup>23</sup>. Comparison of the effect of loading dose on the frequency of CIN between atorvastatin and rosuvastatin in patients with STEMI undergoing PCI (atorvastatin 80 mg (n=98) or rosuvastatin 40 mg (n=94) before the procedure) showed that the incidence of CIN was 8.9% (n=17) in all groups. It was determined that only the amount of contrast agent administered is an independent predictor for CIN, while the ejection fraction (EF) of the left ventricle showed marginal statistical significance. This study showed that atorvastatin and rosuvastatin had similar efficacy in the prevention of CIN in patients with STEMI undergoing PCI<sup>24</sup>. The prophylactic effect of rosuvastatin and atorvastatin on CIN in patients with CKD undergoing PCI (rosuvastatin 10 mg, and atorv-

astatin 20 mg) was also prospectively compared. CIN was observed in 58 (5.4%) patients. In general, it was concluded that rosuvastatin and atorvastatin have similar efficacy for the prevention of CIN in patients with CKD who underwent PCI. In general, the analysis of the conducted studies shows that atorvastatin may have the strongest renal protective effects. But there are still a lot of questions in individual categories of patients with ACS, dependence on the duration, age of patients, EF, the left ventricle (LV) volume, and LV diastolic function.

Clinical studies with atorvastatin have found a significant reduction in cardiovascular events in patients with and without CAD. Studies show that a high dose of atorvastatin will reduce LDL to about 70 mg/dL in many patients and improve heart outcomes. Available research data suggest that a high dose of atorvastatin may stop and cause an atherosclerotic progression to regress. Studies of the effects of statins in patients with diabetes have shown that atorvastatin reduces the occurrence of acute, clinically significant cases of CAD, coronary revascularization, and stroke. Atorvastatin is effective in reducing nonfatal myocardial infarction and fatal CAD in hypertensive patients with three or more additional risk factors. A high dose of atorvastatin is effective in elderly patients who have recently undergone STEMI and to slow down the cognitive decline in preliminary studies in Alzheimer's patients. Limitations of this review include the lack of generalizability of atorvastatin research data for other statins, the lack of tests for initial brain results involving newer statins, and relatively short study durations (none exceed 5 years) while atherosclerosis is usually a long-term illness. A convincing body of evidence suggests that atorvastatin reduces major cardiovascular events in both secondary and primary prevention of CAD. Besides, atorvastatin is safe and well-tolerated throughout the entire dose range<sup>25</sup>. It should be noted that several studies have shown the additional effect of statins on slowing the progression of diabetic nephropathy. However, few reports directly compare the renal protective effects of active and normal statins.

CKD has been proven to be associated with inflammation. The effect of atorvastatin on inflammatory biomarkers was evaluated in patients with CKD in a LORD study. In patients with elevated baseline IL-6/8/10 and/or pentaxin-3 (PTX3) plasma levels, a decrease in GFR during the study was significantly lower in patients who received atorvastatin compared with placebo, while those with no inflammatory biomarkers showed no differences. Patients receiving placebo with elevated levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) did not have a decrease in GFR, whereas patients receiving atorvastatin had a decrease in their GFR. Large-scale studies with statin therapy, particularly in patients with inflammation-related CKD, may be useful for studying<sup>26</sup>. Since dyslipidemia is an independent risk factor for CKD progression, then the - absorbing therapy may be potentially associated with inhibition of CKD progression. A clinical benefit assessment in patients with CKD with atorvastatin was developed to determine whether ator-

vastatin has a protective effect on kidney function in patients with dyslipidemia and CKD. This study differs from similar ones by an increase in statistical accuracy obtained from its much larger sample size and longitudinal value<sup>27</sup>.

It has been suggested that the renal protective effects of statins may be the result of effects on endothelial cell function. Nitrogen oxides (NO) mediates endothelial vasodilation and also contributes to both natriuresis and diuresis by increasing renal blood flow and GFR<sup>28</sup>. NO also increases renin secretion<sup>29</sup>. Statins have been shown to improve the activity of basal nitrogen oxides (NO) and nitrogen oxide-dependent endothelial vasodilation in healthy volunteers and patients with heart disease<sup>30</sup>. There is currently no effective strategy to prevent impaired renal function, and therefore the renal protective effects of statins are of promising importance. Atorvastatin increases the availability of nitrogen oxides (NO), prevents the formation of oxygen free radicals and reduces the regulation of expression of cyclooxygenase 2<sup>31</sup>.

A significant trial of Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) has found that suppression of low-grade inflammation with statins (rosuvastatin) improves clinical outcome in the subjects without CAD. We should also note a smaller number of adverse effects when using rosuvastatin 10 mg/day compared with the more intensive rosuvastatin regimen in Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)<sup>32</sup>. Also, by modern clinical guidelines for the treatment of dyslipidemia, intensive statin regimens are considered impractical for people older than 75 years due to an increased risk of adverse effects<sup>33-38</sup>.

**Summary:** The anti-inflammatory effect of statins is well known and may have relevance to their renal protective effects. By inhibiting the formation of intracellular isoprenoids, statins inhibit vascular and myocardial inflammation, modulate vascular and myocardial redox state favorably and improve the bioavailability of nitric oxide. Thus, currently available data suggest that the use of statins has a positive effect on the level of lipids in the blood of elderly people. Due to the increase in the share of elderly and senile people in Russia, as well as the high mortality from CVD complications, many elderly people in our country may have strong clinical reasons for choosing statins as a basic lipid-lowering therapy.

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